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THE SYNTHESIS OF o-HYDROXYALDEHYDES

by

Lawrence M. Liggett

A Thesis Submitted to the Graduate Faculty
for the Degree of

DOCTOR OF PHILOSOPHY

Major Subject: Analytical Chemistry

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INTRODUCTION

The present investigation was undertaken in an effort to find a more satisfactory method for the synthesis of o-hydroxyaldehydes, and to prepare in moderate quantity a large number of these aldehydes which were required for other investigations being conducted in the Chemistry Department at Iowa State College. A survey of several existing methods was made and a critical study of two of these undertaken in an effort to improve yields and in general to provide a convenient laboratory method for the preparation of these compounds. A large number of o-hydroxyaldehydes have been prepared, many of which have not been previously reported in the literature.

METHODS FOR THE SYNTHESIS OF o-HYDROXYALDEHYDES

The Reimer-Tiemann Reaction

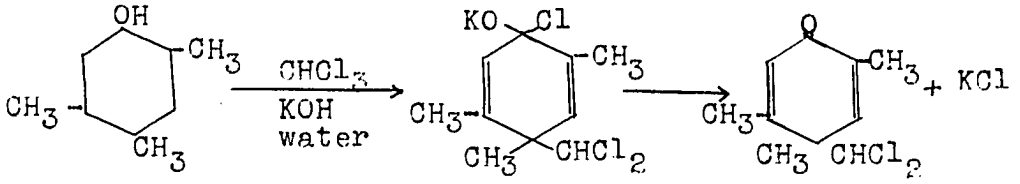
The reaction involving carbon tetrachloride or chloroform on a phenol in alkaline solution was first suggested by Reimer and Tiemann (1) as a general method for the preparation of ortho and para hydroxybenzaldehydes and the corresponding acids. When chloroform was employed o-hydroxyaldehydes were the principal product, while with carbon tetrachloride, p-hydroxybenzoic acids were obtained. This method has proved to be very general in its applications and most of the o-hydroxyaldehydes reported in the chemical literature have been prepared by the method of Reimer and Tiemann.

Early in this research, several o-hydroxyaldehydes were prepared by this method and it was found that the procedure was long and the yields small and that it was not a satisfactory method for the preparation in moderate quantities of the large number of o-hydroxyaldehydes needed. Accordingly, a survey of the mechanisms which have been proposed for this reaction was made with the hope that a basis for further experimental work would be found which might lead to improved yields and in general a more satisfactory method.

One of the earlier attempts to elucidate a satisfactory explanation for the rearrangement of phenol ethers was the theory of Lapworth (2) which proposed that such rearrangements occur through an α , γ -shift to form an o-substituted phenol. Such rearrangements might possibly occur in the Reimer-Tiemann reaction. The reactions based on such a mechanism are outlined below and involve the elimination of sodium chloride between the alkali phenolate and chloroform to give a dichloromethyl ether, followed by an α , γ -shift of the dichloromethyl group to the o-position. Similarly by successive shifts, substitution in the p-position might occur.

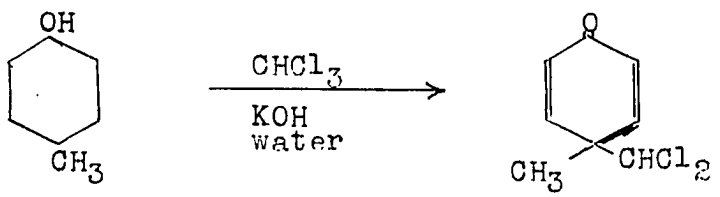
Auwers and Winternetz (3) have indicated that a compound 1,2,4-trimethyl-2-dichloromethyl-5-ketodihydroben-

zene, I, is formed in the Reimer-Tiemann reaction on pseudo-cumenol rather than the anticipated o-aldehyde.



I

As shown in the equation above, these authors have suggested that the reaction may take place through a 1-4 or 1-2 addition of chloroform followed by the elimination of alkali chloride. Of special interest was the dichloroketone, II, identified by these authors as one of the principal products from the reaction involving p-cresol.



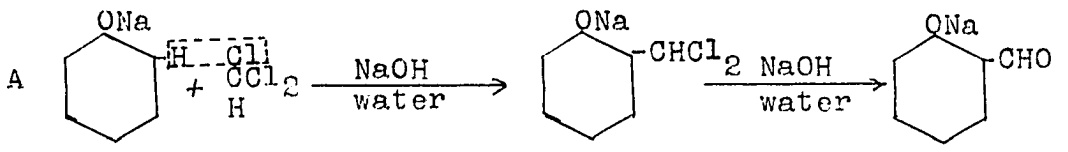
II

It was shown that many ortho- and para-alkylated phenols gave similar products in yields of 40 per cent or more. It would appear, therefore, that these alkyl substituents have enhanced the reactivity at these centers rather than

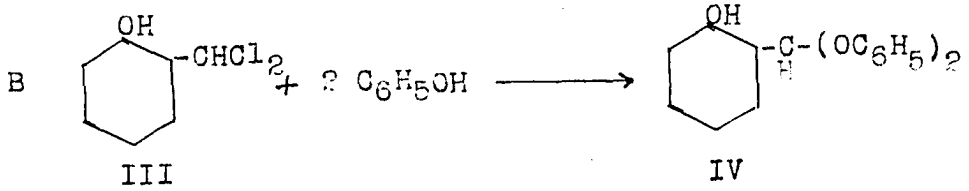
blocked these positions, as would be expected. It is significant that phenol itself and also all negatively substituted phenols have been found not to form compounds with structures similar to those shown above. Also the normal reaction proceeds hardly at all on these negatively substituted phenols and the yields of aldehydes are extremely small. The addition mechanism may explain the formation of these ketones and in part the low yields of aldehydes, but it does not provide an explanation of the mechanism for the formation of the o-hydroxyaldehydes.

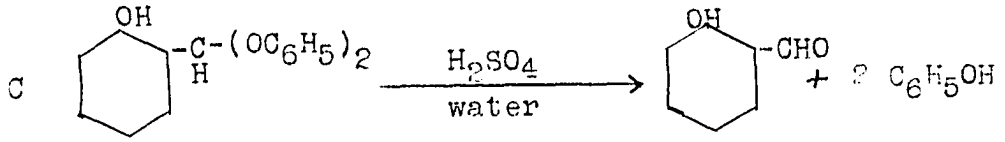
An adequate mechanism for the Reimer-Tiemann reaction, in addition to the experimental facts just given, must explain also the very low yields of aldehydes obtained and the large amounts of unchanged phenols that are recovered from the reaction products.

The simplest mechanism which one might formulate involves direct C-alkylation (4,5). In this manner hydrogen chloride is eliminated between an ortho- or para-nuclear hydrogen atom and chloroform, followed by hydrolysis of the dichloromethyl phenol to an aldehyde.



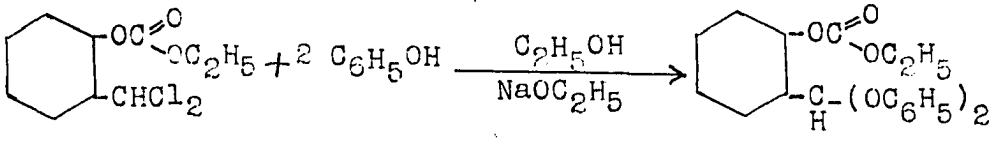
This mechanism in itself does not completely explain all of the known experimental facts. Armstrong and Richardson (4) however have further postulated that if an intermediate such as hydroxybenzalchloride, III, is formed in the reaction that this might lead to the formation of an acetal, IV, by further reaction with part of the phenolic compound.



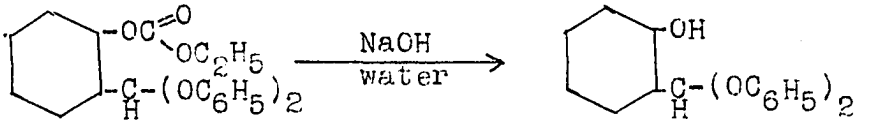


In this manner two-thirds of the phenol would be used in the acetal formation and would be recovered along with any aldehyde formed upon acidification and steam distillation. Such a mechanism would logically explain both low yields of aldehydes and recovery of a major portion of the phenol. Attempts by these authors to prepare o-hydroxybenzalchloride, III, failed, but they succeeded

in preparing carbethoxysalicylaldehydediphenylacetal, VI, from o-ethylcarbonatobenzalchloride, V, and then by alkaline hydrolysis obtained salicylaldehydediphenylacetal, VII. This last product was found to be stable in strong alkali, but was readily hydrolysed by acids, even by sodium bicarbonate, which agrees with the experimental conditions for the Reimer-Tiemann reaction.



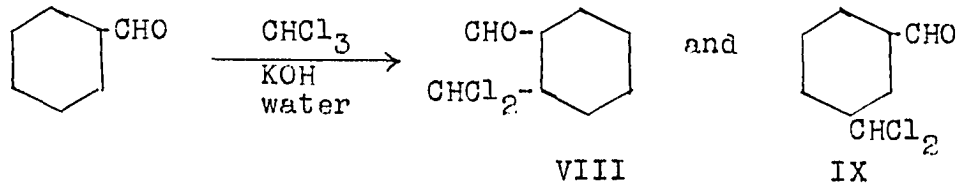
V VI



VI VII

The only point not substantiated by experimental evidence in the mechanism of Armstrong and Richardson is the formation of a dichloromethylphenol, III, above. That such a compound might well be formed by direct C-alkylation at the ortho and para positions which are activated by the hydroxyl group seems probable, but unfortunately such a compound has not been isolated. There is still an abundance of evidence supporting the view that the formation of a dichloromethylphenol is the initial step in this

reaction. Recent work by Chaudhuri (6) has shown that compounds of this type are formed in the Reimer-Tiemann reaction on benzaldehyde.



VIII IX

The isolation and identification of VIII and IX provides more direct evidence that dichloromethylphenols may also be intermediates in this same reaction on a phenol.

Although all other mechanisms cannot be precluded, most of the experimental facts seem best explained by the mechanism of Armstrong and Richardson which proposes that the Reimer-Tiemann reaction involves the reaction of an alkali phenolate with chlorofcrm by direct C-alkylation to yield an intermediate dichloromethylphenolate which in turn may react with more phenolate, resulting in the formation of an acetal. Hydrolysis of the acetal in acid medium yields ortho- and some para-hydroxyaldehyde, and in addition a considerable amount of the original phenol. These reactions have been adequately summarized by reactions A, B, C, on pages 5 and 6.

From a practical viewpoint, the Reimer-Tiemann reaction as a general method for preparing ortho- and

para-hydroxyaldehydes is seriously handicapped by the very low yields obtained and the several time consuming operations necessary to carry out the synthesis. Numerous investigators have attempted to modify the procedure in various ways in an effort to improve the yields and shorten the time required.

The various alkali and alkaline earth hydroxides and also their carbonates have been used alone and in mixtures as the alkali. No advantage was obtained from these modifications. Various solvents have been employed in order to obtain a more homogeneous reaction mixture. Sen and Ray (7) have stated that when the alkali salt of the phenol being employed is sparingly soluble in the usual caustic solution, as for example o-halogenphenols and 2-hydroxyanthraquinone, that the yields may be considerably improved by employing a water, pyridine, and alcohol mixture as solvent. Armstrong and Richardson (4) however are of the opinion that the non-homogeneity of the reaction mixture is not the explanation for low yields, for in substituting trichloroacetic acid for chloroform they obtained no better yields of aldehydes from phenol, alkylated phenols, m-nitrophenol, and chlorophenols.

Hodgson and co-workers (8, 9, 10, 11, 17) have made

a detailed study of the effect of negative substituents on the directive influence exerted by the hydroxyl group in the Reimer-Tiemann reaction. For example, the influence of fluorine in the meta- position produced a deactivation of the para- hydrogen and the ratio of ortho- to para- hydroxyaldehyde is greater than with phenol itself. Upon replacing chloroform in the Reimer-Tiemann reaction by bromoform, Hodgson and Jenkinson (8) have shown that only a slight variation in the ratio of ortho- to para- substitution occurs, and that the total yields are not affected. With ortho- substituted phenols lower o-/p- ratios resulted with bromoform than with chloroform, but the reverse was true in the case of meta- substituted phenols.

In general it may be stated that with phenol and various alkyl substituted phenols the o-hydroxyaldehyde is produced in considerably greater quantity than the para- isomer. Separation of the isomers may usually be accomplished by steam distillation owing to the volatility of the o-hydroxyaldehyde with steam. A bisulfite extraction is necessary to separate the aldehyde from the phenol which also steam distills. When two o-hydroxyaldehydes are produced, as for example in the Reimer-Tiemann reaction of m-cresol, other methods of separation must be employed (12, 13).

The yields obtained by this reaction as previously mentioned are very low, varying from two per cent or less up to twenty per cent. The nature of the phenol employed seems to determine the yield obtained, ortho- substituted phenols giving the lowest yields. The writer is aware of but two exceptions to the previous statement. One of these is the reaction on β-naphthol (14). In this instance the expected 2-hydroxy-1-naphthaldehyde is produced in yields of ninety per cent. The other exception is the case of 4-hydroxybiphenyl (15, 16) where an eighty per cent yield of 4-hydroxy-3-aldehydobiphenyl was reported.

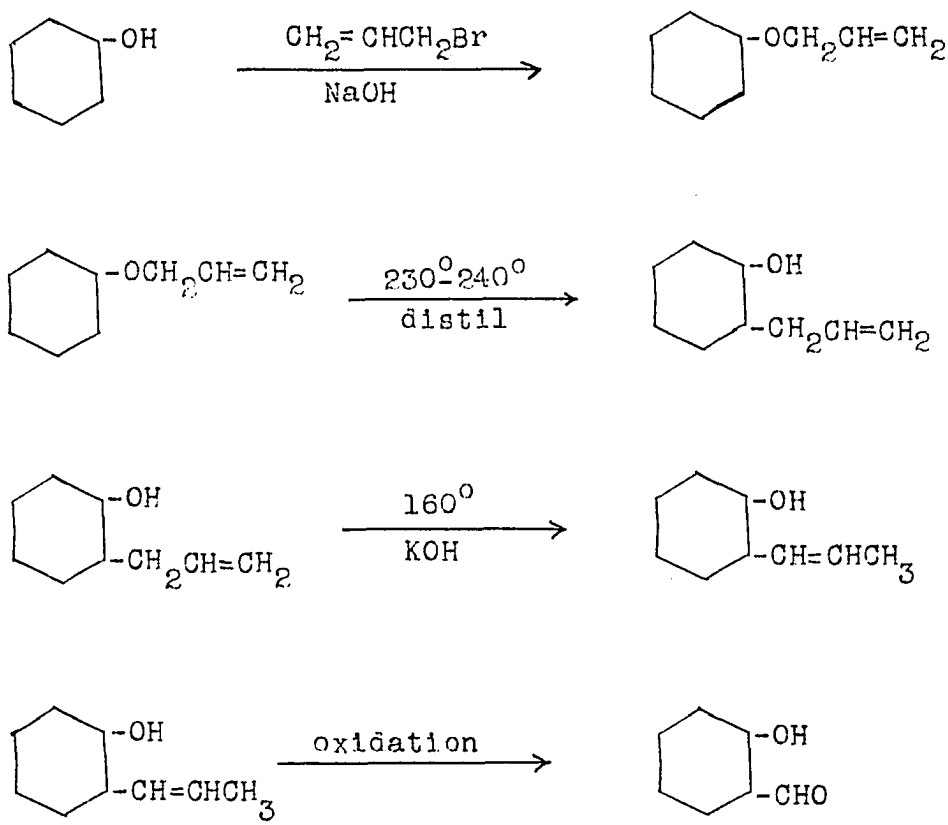
Further studies on this reaction have been made in an effort to increase the yields obtained and these results are reported in the experimental part of this thesis. This work consisted in studying the effect of varying the amounts of the reagents and the order of addition of reagents. Studies were also made on the effect of higher temperatures made possible by conducting the reaction under pressure.

Allyl Rearrangement Method

The allyl rearrangement method has been used to a very limited extent as a laboratory synthesis of o-hydroxy-aldehydes. This method involves four principal steps,

namely, preparation of the allyl ether of the phenol, rearrangement to the o-allylphenol, isomerization to the o-propenylphenol, and finally, oxidation of the propenyl group to an aldehyde.

These reactions are as follows:

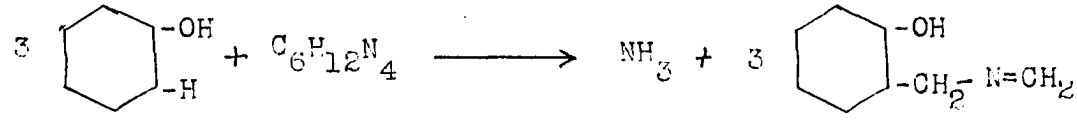


Claisen (18) has applied the first three of the above four steps to a very large number of phenols. The yield in each of these steps is very good and an ultimate conversion

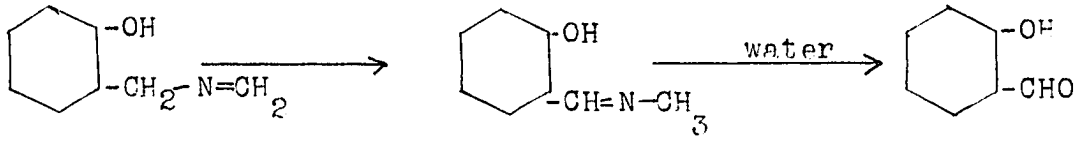
of phenol to o-propenylphenol corresponding to about ninety per cent of theoretical has been realized. Conditions which are generally applicable for the last step in this synthesis, which involves oxidation of the propenyl group to an aldehyde, have not been reported, and in addition the time required for a completed synthesis is too long to be considered a convenient laboratory method.

The Duff Reaction

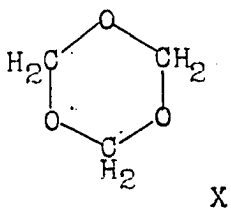
Recently Duff (19) described a new and apparently general method for the preparation of o-hydroxyaldehydes from phenols by reaction with hexamethylenetetramine. The synthesis consisted essentially in causing hexamethylenetetramine and a phenol to react in the presence of anhydrous glycerol and glyceroboric acid at a temperature of 150-160°. The o-hydroxyaldehyde in very nearly pure form was obtained by steam distillation of the acidified reaction mixture. No bisulfite extraction was necessary, and in most cases no unreacted phenol was recovered. This synthesis was more rapid and gave better yields of a purer product than the Reimer-Tiemann method. Duff (19) has suggested that the mechanism of this reaction might be



followed by isomerization and hydrolysis



The only experimental evidence in favor of such a mechanism is that it was found necessary to carry out the reaction in an anhydrous medium to prevent hydrolysis of the hexamethylenetetramine to formaldehyde, in which case aldehydes are not produced. Support for the view that formaldehyde is not involved in the reaction was found by Schwandt and Diehl (20) who substituted trioxane, X, for hexamethylenetetramine in this reaction. In the presence of an acid catalyst, trioxane decomposes to give formaldehyde. No o-hydroxyaldehyde was formed in this reaction. Further evidence is the fact that isomerizations of the type proposed above are in general favored by a high reaction temperature. Duff reported the reaction to require five to six hours when carried out in glacial acetic acid; b.p.: 118°, as compared to fifteen minutes when carried out in the glyceroboric acid mixture at 160°.



X

The method of Duff was made the object of a more

critical study in an effort to determine the optimum conditions for the reaction and to improve the yields. The details of this work and the subsequent preparation of numerous o-hydroxyaldehydes are reported in the experimental part of this thesis.

EXPERIMENTAL WORK

Studies on the Reimer-Tiemann Reaction

The literature reviewed has revealed that although many slight modifications of the Reimer-Tiemann reaction have been tried, no systematic study has been made of the effect of varying the amount of the various reagents used over a considerable range in order to determine the optimum concentrations for the reaction. In the following described series of experiments, each of these variables was changed, one at a time, and over a wide range. The phenol employed in all of these studies was o-ethoxyphenol, a good grade of which was obtained from Monsanto Chemical Company, b.p.: 213°/742 mm.; m.p.: 27°. This particular phenol was employed for two reasons. First, a considerable quantity of this phenol was on hand, having been obtained from Monsanto in another connection. Second, many of the aldehydes which it was desired to prepare, subsequent to

finding a more satisfactory method for their synthesis, were to be prepared from various ortho- substituted phenols. Baker & Admanson, C.P. grade sodium hydroxide was used throughout these experiments. The chloroform used was U.S.P. grade obtained from the Mallinckrodt Chemical Works.

Series I. In this series, five Reimer-Tiemann reactions were run under identical conditions, the only variable being the amount of chloroform employed. The reactions were run in five liter, three necked flasks fitted with a dropping funnel and a Hopkins condenser. Each reaction was carried out using 110 g. (0.8 moles) of o-ethoxyphenol, 2500 ml. of water, and 256 g. (6.4 moles) of sodium hydroxide. This mixture was brought to a gentle reflux, and then the chloroform added slowly over a period of two to three hours. Only a very low flame was required to keep the mixture refluxing as there was considerable heat evolved during the reaction. It was found necessary to keep the stem of the dropping funnel below the surface of the liquid to prevent flashing of the chloroform from the surface of the hot aqueous solution. After all of the chloroform had been added, the mixture was refluxed for an additional three hours. At the end of this time any remaining chloroform was allowed to escape through the reflux condenser. The mixture was then cooled and a liter of cold 15 per cent

sulfuric acid added. The mixture was then steam distilled until no more oil separated from the cold distillate. Usually two or more liters of distillate were collected. The oil which separated from the distillate consisted of the desired 2-hydroxy-3-ethoxybenzaldehyde and unchanged o-ethoxyphenol. The yield of aldehyde was estimated by a method which will be described in a later section. In the above series of five reactions the amount of chloroform was varied from 0.8 mole to 8.0 moles. Table I summarizes the yields obtained on this first series of reactions.

TABLE I

Yields Obtained in the Reimer-Tiemann Reaction
By Varying Amount of Chloroform Used

Chloroform Moles	Yield of Aldehyde Per Cent
0.8	2.0
1.6	2.0
3.2	6.4
5.6	4.5
8.0	5.1

It was concluded from the above work that 3.2 moles of chloroform per 0.8 mole of the phenol, or a ratio of 4 to 1, was optimum. This was supported further by the

fact that a considerable amount of chloroform remained even upon prolonged refluxing, when larger amounts of chloroform were used. It should be mentioned that this 4 to 1 ratio of chloroform to phenol might be affected by large changes in the alkali concentration. It was hoped that this effect would not be appreciable if a considerable excess of alkali was employed.

Series II. Four reactions were run as described in Series I. In this series, 0.8 moles of o-ethoxyphenol, 3.2 moles of chloroform, which was the optimum ratio found in Series I, and 2500 ml. of water were used. The alkali concentration was varied from 2.4 moles to 9.6 moles. In Table II are summarized the results obtained from this group of reactions.

TABLE II

Yields Obtained in the Reimer-Tiemann Reaction

By Varying Alkali Concentration

Sodium Hydroxide Moles	Yield of Aldehyde Per Cent
2.4	6.5
4.8	7.0
7.2	7.7
9.6	8.4

It was found that increasing the amount of alkali above

9.6 moles produced no further increased yield of aldehyde. However it was found possible to decrease both the amount of alkali and water to 6.4 moles and 1500 ml. respectively without decreasing the yield of aldehyde below 8 per cent.

Several other reactions were run on the basis of the above ratios, in which the time of refluxing was prolonged up to 12 hours. In no instance was the yield above 9 per cent.

Sen and Ray (7) have indicated that the use of a mixture of water, pyridine and alcohol as a solvent in the Reimer-Tiemann reaction on o-bromophenol increases the yield of aldehyde. Two attempts to repeat this work using o-chlorophenol failed completely, no aldehyde whatsoever being obtained. Stuckwisch (21) has found that the results of Sen and Ray (7) on o-chlorophenol could not be duplicated.

Although it appeared from the preceding work that nearly optimum conditions had been found, the yields obtained were still far from satisfactory. It will be observed that the temperature of this reaction is fixed by the boiling point of the aqueous medium and that of the chloroform, the temperature of the reaction interface probably lying between the two boiling points. The effect of a higher reaction temperature made possible by carrying out the reaction under pressure was thought worthy of

consideration. Accordingly an autoclave was procured and several reactions run at considerably higher temperatures.

Pressure Reactions. The autoclave used was constructed of iron and was of 4 liters capacity. It was gas fired, and was equipped with a thermometer well, a two-bladed hand stirrer, and a safety valve set at 250 p.s.i.g.

Pressure Reaction I. A quantity of 140 g. (1 mole) of o-ethoxyphenol was dissolved in 2 liters of water in which had been dissolved 320 g. (8 moles) of sodium hydroxide. 480 g. (8 moles) of chloroform was then added and the autoclave sealed. The mixture was heated and stirred continuously. When the pressure reached 75 p.s.i.g., the heating was discontinued as the pressure continued to rise quite rapidly until 150 p.s.i.g. was reached. The stirring was continued for more than an hour, and then the pressure released and any excess chloroform allowed to boil off. The mixture was steam distilled as previously described. The yield of aldehyde was 12 per cent.

Pressure Reaction II. This reaction was carried out using the same quantities as described above. After the pressure reached 75 p.s.i.g. the heating was discontinued but the pressure increased rapidly and reached

175 p.s.i.g. in about 10 minutes. Rather than continuing the heating and stirring at this point as was done in the previous experiment, the pressure was immediately released and the reaction discontinued. It was hoped that this might decrease the amount of tar formed. The yield of aldehyde in this reaction was about 13 per cent.

Pressure Reaction III. This reaction was conducted as described in the two previous experiments except that the pressure was maintained at 230 p.s.i.g. for more than an hour. The mixture was stirred continuously during this period and a small amount of heat was required after the initial reaction had subsided. The product from this reaction was 150-160 grams of a semisolid tar, from which only a trace of aldehyde was obtained.

It was concluded from the above work that pressures much above 175 p.s.i.g. are entirely unsatisfactory, and that although yields are slightly improved by carrying the reaction out under a moderate pressure, the advantage does not warrant the extra labor involved.

Estimating 2-hydroxy-3-ethoxybenzaldehyde in the presence of o-ethoxyphenol. As has been previously stated, the crude product from a Reimer-Tiemann reaction always contains a large amount of the original phenol along with the o-hydroxyaldehyde. Perhaps as objectionable a feature of this reaction as the low yields, are the cumbersome,

time-consuming operations of purifying the crude product. The method most frequently used by other workers (1, 3, 12) has been to extract the steam distillate with ether, remove any aldehydes by bisulfite extraction of the ether solution, decompose the bisulfite solution with dilute mineral acid, and finally obtain the pure o-hydroxyaldehyde by steam distillation of the decomposed bisulfite solution. Even this procedure has its limitations. First, repeated extraction of the ether solution, using dilute bisulfite solutions, is necessary to obtain all of the aldehyde. This is necessary since the formation of any solid bisulfite addition product must be avoided because it is easily contaminated with the phenol and cannot be washed free from this impurity (12). Secondly, several aldehydes do not form bisulfite addition products, as for example o-thymolaldehyde, and o-carvacrolaldehyde (19). The experimental work previously described was entirely concerned with improving the yields of the Reimer-Tiemann reaction, not in obtaining the pure 2-hydroxy-3-ethoxybenzaldehyde which is available commercially. Therefore a method was needed for estimating the amount of aldehyde produced without necessarily isolating the pure material.

Fractional distillation was first attempted. The vapor pressure vs. temperature relationship of o-ethoxy-

phenol and for 2-hydroxy-3-ethoxybenzaldehyde was determined. Fractionation of a known mixture of these two compounds was then attempted.

Pressure-Temperature Relationship of o-ethoxyphenol and 2-hydroxy-3-ethoxybenzaldehyde. For this work, two 250 ml. Claisen flasks were set up for vacuum distillation. Each was connected to a condenser and receiver. The two receivers were interconnected to the same manometer, dry ice trap, and vacuum pump, so that identical pressures prevailed in each distillation system. Pure o-ethoxyphenol was placed in one flask; b.p.: 213°(corr.)/742 mm.; m.p.: 27°. In the other, pure 2-hydroxy-3-ethoxybenzaldehyde, b.p.: 265°(corr.)/742 mm.; m.p.: 65°, was placed. Both the phenol and aldehyde were obtained from Monsanto Chemical Company. The distillation of both materials was carried out simultaneously. The pressure was decreased gradually, and with the aid of another observer, the temperatures and pressure on both systems were observed at the same time. The data obtained are summarized in Table III. The temperatures in this table are uncorrected. For greater convenience the data are plotted in graphical form in Figure 1, page 25.

TABLE III

Vapor Pressure-Temperature Relationship of

o-Ethoxyphenol and 2-Hydroxy-3-ethoxybenzaldehyde

Absolute Pressure mm. Hg.	Boiling Point of Phenol	Boiling Point of Aldehyde	B. P. T.
7	96°	118°	22°
38	119	159	40
113	145	188	43
374	182	225	43
618	200	247	47
742	208	255	47

Fractional distillation of a mixture of o-ethoxyphenol and 2-hydroxy-3-ethoxybenzaldehyde. Since both the phenol and aldehyde decompose slightly upon distilling at atmospheric pressure, vacuum fractionation was necessary. By referring to Table III it will be seen that at 38 mm. the boiling point differential is 40°, which should enable a good separation to be accomplished without danger of much decomposition. A mixture containing 108 g. of the phenol and 150 g. of the aldehyde were fractionated using a 14 in. air cooled Vigreaux column. A first fraction of 120 g. was collected; b.p.: below 145°/40 mm. A refractionation of this portion yielded 100 g. of nearly pure o-ethoxyphenol; b.p.: below 150°/160 mm. This corresponded to a recovery of 92 per cent of the phenol in the original mixture.

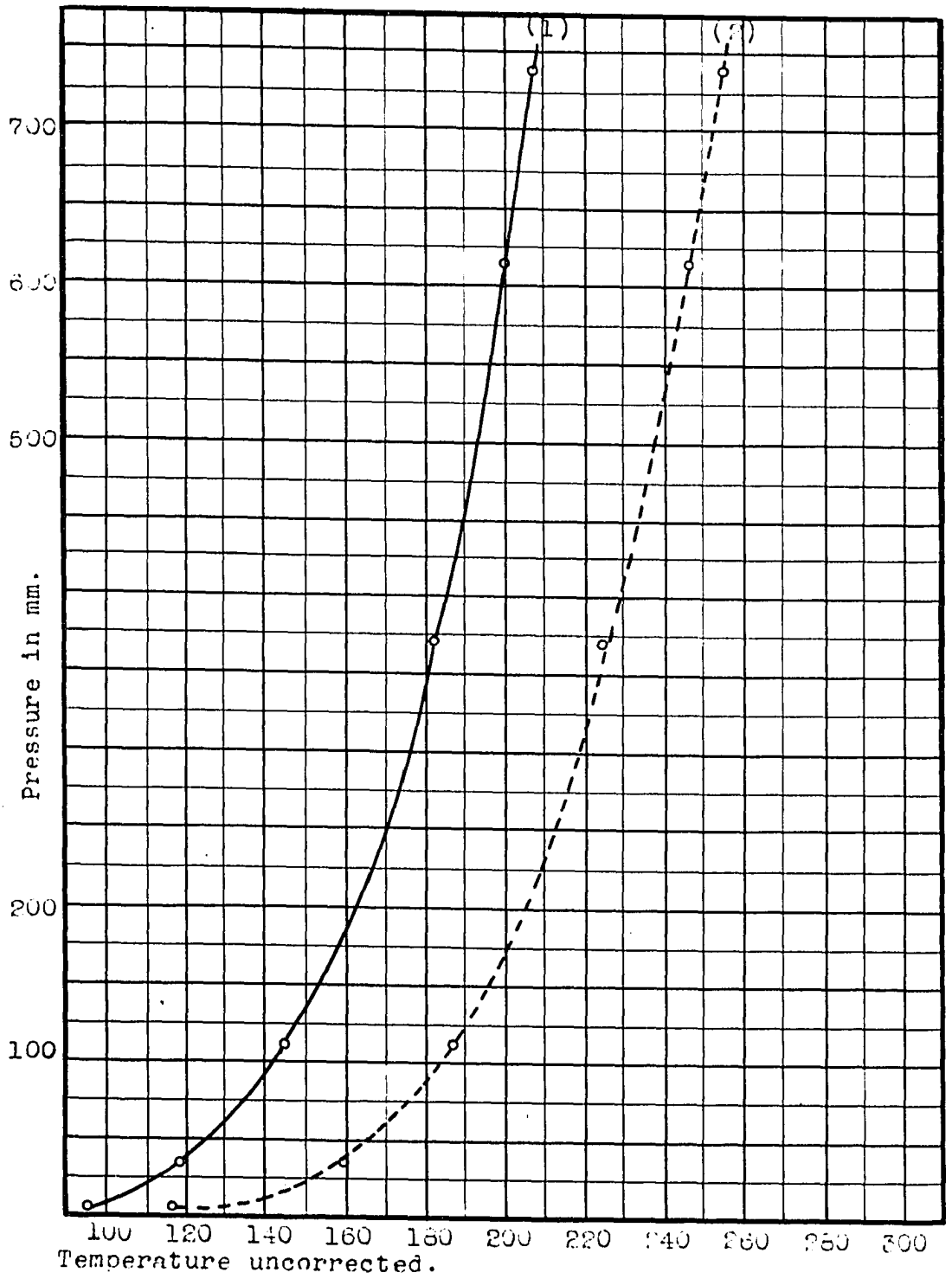


Figure 1.
Vapor Pressure Curve For o-Ethoxyphenol (1)
and 2-Hydroxy-3-ethoxyBenzaldehyde (2)

By the use of a more efficient column a better separation undoubtedly could have been obtained. This was not attempted since the crude yields from the Reimer-Tiemann reactions only gave about 50 g. of material, only 10 per cent of which was aldehyde, and this amount was not considered sufficient material to carefully fractionate and obtain complete separation of the two components.

In a search for a more convenient method of estimating the amount of aldehyde in the phenol-aldehyde mixtures, it was found that the Schiff's base of the aldehyde with ethylenediamine, crystallized in good yield from a dilute alcohol solution, even in the presence of considerable amounts of the phenol. This fact was therefore made the basis of an analytical method for estimating the yields of aldehydes from the previously described Reimer-Tiemann reactions. The method was first applied to a series of known aldehyde-phenol mixtures.

Separation of an aldehyde by means of its Schiff's base with ethylenediamine, from an aldehyde-phenol mixture. Known mixtures of pure 2-hydroxy-3-ethoxybenzaldehyde and o-ethoxyphenol were prepared, each containing 25 g. of the aldehyde. Each mixture was dissolved in exactly 100 ml. of 95 per cent alcohol and 125 ml. of water added. The mixture was then heated to 80° and a solution of ethylenediamine, 6 ml. of 66 per cent ethylenediamine

in 25 ml. 95 per cent alcohol was added. The solution was stirred for a minute or two and then allowed to stand for three hours after cooling to 20°. The Schiff's base separated immediately from mixtures containing small amounts of phenol, but much more slowly when large amounts of phenol were present. After standing and cooling as specified above, the Schiff's base was filtered on a small Buchner funnel, washed once with 20 ml. of ethanol cooled to 0-5°, sucked as dry as possible, and then dried in air at 90°. When dried, the Schiff's base was weighed, which served as a measure of the aldehyde originally present. Table IV summarizes the results obtained on the series of known mixtures.

TABLE IV

Separation of 2-Hydroxy-3-ethoxybenzaldehyde from o-Ethoxyphenol by means of its Schiff's Base with Ethylenediamine

Phenol Present	Aldehyde Present	Schiff's Base Obtained
None	25 g.	22.5 g.
5 g.	" "	22.5
25	" "	22.5
50	" "	22.5

Theoretical yield of Schiff's base is 27 g., and it was therefore necessary to apply a correction factor. This

method can only be considered reliable when conditions are carefully standardized since the solubility of this Schiff's base in alcohol is appreciable. The method might have been improved by using o-phenylenediamine in place of ethylenediamine, which forms a Schiff's base with the aldehyde which is less soluble in dilute alcohol.

In determining the yields of aldehydes on the reactions previously described it was found advisable to remove part of the phenol by fractionation prior to separation of the aldehyde as the Schiff's base. This was deemed necessary since in such mixtures the ratio of phenol to aldehyde was usually about 5 to 1.

Studies on the Duff Reaction

Early experience with this reaction did not give results as good as reported by Duff (19). In some cases the reaction was found to progress smoothly while in other instances a rather violent reaction ensued when the hexamethylenetetramine and phenol were added to the hot glyceroboric acid. This made it almost impossible to control the temperature within the range 150-160° as specified. More perplexing was the fact that in several instances on duplicate preparations, a very good yield was obtained from one reaction and a very poor yield on

the other. In some cases no aldehyde was obtained although the same procedure had been followed. The difficulty was finally traced to the fact that the hexamethylenetetramine when added to the glyceroboric acid medium at a temperature much above 160° decomposes very rapidly. Therefore if the phenol is not added immediately, no aldehyde will be formed. A very marked improvement in the yields was obtained by mixing the hexamethylenetetramine and phenol intimately, thereby adding them simultaneously to the glyceroboric acid medium. Vigorous stirring of the viscous mixture was found to be necessary.

In general it was found possible to control the temperature between 150-160° as specified by Duff merely by removing the reaction beaker from the electric hot plate prior to adding the phenol-hexamethylenetetramine mixture, and then heating again if necessary after the initial reaction had subsided. A cooling bath was always at hand for use in case the reaction became violent. This seldom happened when the glyceroboric acid mixture was cooled to 150° before adding the other reagents. Curtis and Diehl (23) have conducted experiments in which the temperature of this reaction was carefully controlled at 160°. No noticeable improvement in yields were obtained. From the experience gained in running a large

number of these reactions it seems probable that the temperature may vary between 145-175° without ill effect on yields.

Procedure adopted. The modified Duff procedure which was used in the preparation of most of the aldehydes to be reported in the next section was as follows: A quantity of 300 g. of U.S.P. grade glycerol and 70 g. of boric acid were placed in a two liter beaker and the mixture stirred and heated until the temperature reached 165°. About 20 minutes was ordinarily required for this temperature to be attained since a considerable amount of water must be expelled. A finely pulverized and intimately ground mixture of 50 g. of the phenol and 50 g. of hexamethylenetetramine was then added with vigorous stirring to the hot glyceroboric acid medium at 150°. The reactants were stirred for 20 minutes, and during this period the temperature was maintained between 150-165° by heating or cooling as necessary. Finally the reaction mixture was allowed to cool to 115° and 50 ml. of concentrated sulfuric acid in 150 ml. of water added.

Two methods have been found satisfactory for the isolation of the o-hydroxyaldehydes from the above reaction mixture. The method most frequently employed consisted in steam distillation of the acidified reaction mixture.

Removal of aldehyde by this method is hastened by the fact that the viscous reaction mixture may be heated to about 110-120° while steam is passed through. This was a distinct advantage in the case of difficultly volatile aldehydes. Liquid aldehydes could usually be separated from the distillate by means of a separatory funnel. In some cases extraction with ether or benzene was necessary. Solid aldehydes were filtered off after cooling the steam distillate in an ice bath. When the reaction proceeds in a normal manner, no unreacted phenol is recovered, and the aldehyde is quite pure. The melting point of the crude solid aldehydes were usually only one or two degrees lower than the carefully purified compounds. With difficultly volatile aldehydes it was found more expedient to extract the acidified and cooled reaction mixture directly with ether or benzene, thus avoiding a prolonged steam distillation.

Several advantages over the Reimer-Tiemann method may be claimed for the Duff synthesis. The yields are superior; the average yield on the synthesis of about thirty aldehydes was 18 per cent. The time required for the synthesis is a matter of two or three hours as compared to one or two days for the Reimer-Tiemann reaction. No bisulfite extraction was necessary as the

aldehydes were not contaminated with unreacted phenol. Several phenols were encountered which did not yield aldehydes by the former method, but gave satisfactory yields of the desired aldehyde by the method of Duff. Examples which may be cited are, o-chloro- and o-bromophenol, 2,4-dichloro- and 2,4-dibromophenol. In view of these advantages the Duff reaction was selected for the synthesis of most of the compounds which are reported herein.

It should be mentioned that although the method of Duff has now been found to be very general, several phenols were encountered in the course of this work that did not yield any of the expected aldehydes. These exceptions will be summarized in a later section.

Preparation of Compounds

In this section are described in some detail the syntheses of various aldehydes undertaken during the course of this work. Details of experimental procedure have not been repeated for each preparation. In the case of aldehydes prepared by the Duff reaction, reference will be made to the procedure given in the previous section. The details of one preparation by the Reimer-Tiemann method will be given and used as reference for subsequent preparations which are similar.

2-Hydroxy-5-methylbenzaldehyde. Tiemann and Schotten (12) have described the preparation of this aldehyde from p-cresol and their method is the basis of the procedure described here. Approximately 1 kg. of p-cresol, Eastman Kodak Company P-449, was redistilled and about 600 g. of a middle fraction collected. The water clear product solidified upon standing at room temperature; m.p.: 35°. A quantity of 140 g. of potassium hydroxide was placed in a 1 liter, round bottomed flask, and 300 ml. of water added. The flask was shaken and when all of the potassium hydroxide was dissolved, 45 g. of the purified p-cresol was added and the solution heated just to boiling. The flask was fitted with a reflux condenser and 80 g. of chloroform was added through the condenser by means of a dropping funnel. About 45 minutes was required for the addition of the chloroform and no heating was necessary during this time. The color changed to orange and finally to dark red while the chloroform was added. After all the chloroform had been added the reaction mixture was refluxed for three hours, cooled, and then acidified with 175 ml. of concentrated hydrochloric acid. The mixture was steam distilled until the distillate was clear. The yellow oil which separated from the distillate was extracted with one 100 ml. portion,

and two 50 ml. portions of ether. The entire ether extract was then shaken with two 100 ml. portions of a 10 per cent sodium bisulfite solution followed by an equal volume of a 20 per cent bisulfite solution. The bisulfite extract was placed in a flask connected to a steam generator, and was also fitted with a dropping funnel. The receiver was connected to a water aspirator to remove the sulfur dioxide formed upon acidification of the bisulfite extract. A quantity of 50 ml. of concentrated sulfuric acid was added slowly through the dropping funnel and after the evolution of sulfur dioxide had subsided the mixture was steam distilled. The aldehyde crystallized in the receiver as large yellow plates; m.p.: 52°. A yield of 15 per cent was obtained. Upon recrystallization from 50 per cent alcohol the aldehyde was nearly colorless; m.p.: 55°. Tiemann and Schotten (12) reported 56°. The Schiff's base of this aldehyde and ethylenediamine was prepared; m.p.: 164° from petroleum ether.

2-Hydroxy-4-methylbenzaldehyde and 2-Hydroxy-6-methylbenzaldehyde. Tiemann and Schotten (12) have described the preparation of but one aldehyde from m-cresol. Two o-hydroxyaldehydes would be expected from this cresol. Chuit and Bolsing (13) have prepared these two aldehydes and described a method for their separation.

Eastman Kodak Company m-cresol, P-369, was redistilled and a constant boiling fraction collected. The purified product was water clear; m.p.: 11°. The Reimer-Tiemann reaction on this cresol was run by the procedure just described except that larger quantities were employed. A mixture of the two aldehydes was obtained as a yellow oil from the steam distillation of the bisulfite extract. The yellow oil was separated, dissolved in a sodium carbonate solution containing a slight excess of sodium carbonate, and then steam distilled until no more oil separated from the distillate. The solution was then acidified and the steam distillation continued. The aldehyde obtained from the alkaline distillation could not be crystallized. A phenylhydrazone derivative was prepared and recrystallized from alcohol; m.p.: 168°. Anselmino (22) reported for the phenylhydrazone of 2-hydroxy-6-methylbenzaldehyde; m.p.: 172°. The aldehyde obtained from steam distillation of the acidified solution was a solid; m.p.: 60° after recrystallization from alcohol. Chuit and Bolsing (13), also Anselmino (22), have reported 60-61° for 2-hydroxy-4-methylbenzaldehyde. A phenylhydrazone was prepared; m.p.: 160°. Anselmino reported the melting point of the phenylhydrazone derivative of 2-hydroxy-4-methylbenzaldehyde to be 161°. A mixed melting point with the derivative of

2-hydroxy-6-methylbenzaldehyde was 134°, thus assuring that a good separation of these two isomers had been accomplished. The yield of the two aldehydes was only 10 per cent; about 25 per cent was 2-hydroxy-4-methylbenzaldehyde, and 75 per cent 2-hydroxy-6-methylbenzaldehyde. The Schiff's bases of these aldehydes with ethylenediamine have been prepared and recrystallized from alcohol. The melting point of di-(2-hydroxy-4-methylbenzal)ethylenediimine was 194°, and of di-(2-hydroxy-6-methylbenzal)ethylenediimine, 139°.

2-Hydroxy-3-methylbenzaldehyde. This aldehyde was prepared by the Reimer-Tiemann reaction on o-cresol. A yield of only 5 per cent was obtained on several preparations. The product was a yellow oil; m.p.: 17°. A phenylhydrazone derivative was prepared; m.p.: 93°. Anselmino (24) reported 97° as the melting point of this derivative. The Schiff's base of the aldehyde with ethylenediamine was prepared and recrystallized from absolute alcohol; m.p.: 111°.

Attempted preparation of 2-hydroxy-3-chlorobenzaldehyde. The procedure of Sen and Ray (7) for the modified Reimer-Tiemann reaction on o-bromophenol was followed in this preparation. In this method a mixture of pyridine, alcohol and water is used as solvent. The o-chlorophenol used was obtained from Dow Chemical

Company. Two reactions were run on this phenol but none of the desired aldehyde was obtained. Stuckwisch (21) has reported similar results on this preparation. The preparation of this aldehyde by the Duff reaction will be described later.

2-Hydroxy-5-phenylbenzaldehyde. This aldehyde was prepared in 10 per cent yields by the Reimer-Tiemann reaction on p-hydroxybiphenyl. The method of Bell and Kenyon (16) was followed. The aldehyde was recrystallized from alcohol; m.p.: 100°. The phenylhydrazone derivative was prepared and recrystallized from benzene; m.p.: 210°. Sen and Ray (7) reported 102°, and 210°, for the melting point of the aldehyde and phenylhydrazone respectively.

2-Hydroxy-1-naphthaldehyde. This aldehyde was obtained in very excellent yield by the Reimer-Tiemann reaction on 2-naphthol. The procedure of Fosse (14) which is slightly different from the usual procedure was the basis for this preparation. A quantity of 400 g. of 2-naphthol was dissolved in a solution composed of 1650 ml. of water, 1200 g. of ethyl alcohol and 800 g. of sodium hydroxide. The solution was heated almost to boiling and then 400 g. of chloroform added slowly. The reaction was vigorous and no heating was required while the chloroform was being added. The color changed first to

blue and finally to a light red at the end of the reaction, and the addition of more chloroform or more alkali did not change the color. The alcohol was removed by distillation and the reaction mixture acidified with hydrochloric acid. The crude aldehyde separated as an oil which was extracted with ether, dried over anhydrous sodium sulphate and finally distilled under reduced pressure. The yield was 432 g. or 87 per cent of theoretical; b.p.: 135°/4 mm. The aldehyde was recrystallized from alcohol; m.p.: 81°. The preparation of this aldehyde by nearly the same procedure as described above has very recently been reported by Russell and Lockhart (25). The Schiff's base of this aldehyde with ethylenediamine was prepared and found to be very insoluble in all common organic solvents. Recrystallization was therefore not possible, but the melting point on the material precipitated from an alcohol solution was 312-313° with slight decomposition.

2-Hydroxy-3,6-dimethylbenzaldehyde. Eastman Kodak Company 2-hydroxy-1,4-dimethylbenzene, No. 1153, was used in the synthesis of this aldehyde by the Duff reaction. A yield of 9 g. or 28 per cent was obtained from this reaction using 25 g. of the phenol. The aldehyde was a solid; m.p.: 61° from alcohol. Gatterman (29) reported 62° as the melting point of this aldehyde.

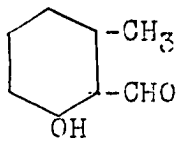
The phenylhydrazone derivative was prepared; m.p.: 148.5° from alcohol. The Schiff's base with ethylenediamine was prepared and gave long yellow needles upon recrystallization from alcohol; m.p.: 182°. Upon prolonged steam distillation of the above reaction mixture a small quantity of white crystalline material was obtained; m.p.: 155°. This material formed a yellow solution in alcohol upon the addition of ethylenediamine but no crystalline Schiff's base was isolated. A crystalline phenylhydrazone was easily prepared; m.p.: 188-190°. It is very probable that this material is a dialdehyde. Duff (19) has reported the formation of several dialdehydes by this reaction on various phenols. Since only a fraction of a gram of the material had been obtained, no further effort was made to identify the product more completely.

Product from the Duff reaction on 4-hydroxy-1,2-dimethylbenzene. The phenol used was obtained from Eastman Kodak Company, No. 1155. The Duff reaction on 25 g. of this phenol yielded 14 g. or 45 per cent of a crystalline product; m.p.: 69° from dilute alcohol. This unusually high yield was at first accounted for by assuming the formation of two o-hydroxyaldehydes. Since this phenol has two open positions ortho to the hydroxyl group the

possibility of forming two isomeric o-hydroxyaldehydes is apparent. A similar case which has been previously discussed were the two aldehydes obtained from m-cresol by the Reimer-Tiemann reaction. Clayton (30) has reported the preparation of two aldehydes, 2-hydroxy-5,6-dimethylbenzaldehyde, and 2-hydroxy-4,5-dimethylbenzaldehyde, by the Reimer-Tiemann method on this phenol. The formation of two such aldehydes has not been previously reported from the Duff reaction. Clayton (30) separated these isomers by hand picking the two crystalline forms which were obtained upon recrystallizing the mixture from petroleum ether. One form was reported to crystallize as needles, and the other as flat plates. Several unsuccessful attempts were made to repeat this work on the product obtained from the Duff reaction, but different crystalline forms could not be distinguished. Another method of separating the two possible isomers was then attempted.

The two isomers, 2-hydroxy-6-methylbenzaldehyde and 2-hydroxy-4-methylbenzaldehyde which were obtained by the Reimer-Tiemann reaction on m-cresol, page 34, were separated by the steam distillation of an aqueous sodium bicarbonate solution from which one isomer was obtained, while the other was obtained by acidification and continued steam distillation. If an analogy with these di-

methylaldehydes is permissible, 2-hydroxy-5,6-dimethylbenzaldehyde, III, and 2-hydroxy-4,5-dimethylbenzaldehyde, IV, might also be separated in the same way. The compound III, corresponding to I, should distil from the alkaline solution.



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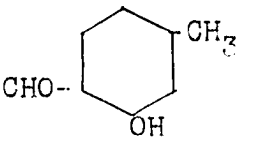

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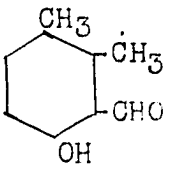
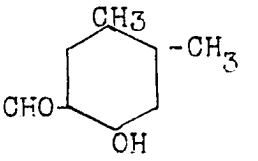


III



IV

This method of separation was attempted. The compound obtained by steam distillation of a sodium carbonate solution of the aldehydes was recrystallized from alcohol and a phenylhydrazone derivative prepared; m.p.: 68°, and of the derivative 198°. The product distilled from the acidified solution was recrystallized and a phenylhydrazone prepared. The melting points were 68° and 198° respectively, and a mixed melting point indicated the derivatives to be identical. These results would seem to indicate that no separation had been accomplished, or

that only one product was originally present. No further effort was made to prove the presence of these two possible isomeric forms.

2-Hydroxy-3,5-dimethylbenzaldehyde. This aldehyde was obtained in 31 per cent yield from the Duff reaction on 2,4-dimethylphenol. The product was an oil at room temperature, but crystallized upon cooling to 3°. Phenylhydrazone and oxime derivatives were prepared. The melting point of the phenylhydrazone was 103°, and of the oxime 133°. Anselmino (24) reported this aldehyde from the Reimer-Tiemann reaction on 2,4-dimethylphenol; m.p.: 11°; b.p.: 222°. Bamberger and Weiler (31) reported the melting point of the oxime derivative to be 138°. The Schiff's base, di-(2-hydroxy-3,5-dimethylbenzal)ethylenediimine, was prepared and recrystallized from alcohol; m.p.: 142.5°.

2-Hydroxy-3-isopropyl-6-methylbenzaldehyde. The preparation of this aldehyde was accomplished by the Duff reaction on thymol. A yield of 56 g. of the crude liquid aldehyde was obtained from the reaction on 300 g. of thymol. Three reactions were run using 100 g. of thymol in each. The crude product was obtained by ether extraction of the steam distillate and removing the ether by distillation after drying over Drierite. The aldehyde was purified by careful fractionation using a Vigreaux

column; b.p.: 105°5 mm.; 100°/3.5 mm.; 139°/13 mm.; 243°/730 mm. with slight decomposition. The refractive index was determined on a sample of boiling point range less than 1°; N_{25}: 1.5506. A semicarbazone derivative was prepared and recrystallized from alcohol; m.p.: 194°. Bell and Henry (32) have reported the semicarbazone derivative of this aldehyde: m.p.: 198°, and the boiling point of the aldehyde to be 110°/115 mm. The Schiff's base of this aldehyde with ethylenediamine was prepared; m.p.: 112-113°. Upon prolonged steam distillation of the reaction mixture about 1 g. of a solid white crystalline material was obtained. This material formed a yellow crystalline Schiff's base with ethylenediamine; m.p.: above 200°. This compound was thought to be a dialdehyde although Duff (19) did not report a dialdehyde from thymol by this reaction. Kobek (33) reported only the formation of the para-aldehyde and a dialdehyde from the Reimer-Tiemann reaction on thymol. Not enough of the compound had been obtained to warrant further investigation.

2-Hydroxy-3-tert-amylbenzaldehyde. A quantity of 500 g. of 2-tert-amylphenol which was obtained from Sharples Chemical Company was fractionated under reduced pressure through a 14 in. Vigreaux column. A 400 g. fraction was collected; b.p.: 147-148°/45 mm. The Duff

reaction on 150 g. of this phenol yielded only 20 g. of aldehyde. The aldehyde was purified by vacuum distillation; b.p.: 106°/10 mm. The Schiff's base of this aldehyde with ethylenediamine was prepared and recrystallized from absolute alcohol; m.p.: 109.5°.

2-Hydroxy-3-methyl-5-tert-amylbenzaldehyde. A sample of 2-methyl-4-tert-amylphenol obtained from Sharples Chemical Company was redistilled and a fraction collected; b.p.: 158-159°/39 mm. The Duff reaction on 200 g. of this phenol yielded 45 g. of a light colored yellow oil. The aldehyde was further purified by distillation; b.p.: 108-110°/1 mm. The Schiff's base of this aldehyde was prepared; m.p.: 90° from absolute alcohol.

Aldehyde from the Duff reaction on 3-methyl-4-tert-butylphenol. A sample of this phenol which had been obtained from Koppers Chemical Company was distilled and a fraction collected; b.p.: 160°/100 mm.; 237-238°/743 mm. Meyer and Bernhauer (34) have reported the boiling point to be 238°. A yield of 50 g. of an aldehyde was obtained from the Duff reaction on 300 g. of this phenol. The product was fractionated, and a portion collected; b.p.: 109-110°/2 mm.; N_{25}: 1.540. Two o-hydroxyaldehydes are possible from this phenol, although from the constant boiling point one might infer that only one compound was present. No attempt was made to prove the presence of

two compounds since no satisfactory method is available for the separation of such isomers. The Schiff's base of this product with ethylenediamine was prepared; m.p.: 165°.

2-Hydroxy-3-chloro-5-tert-butylbenzaldehyde. A sample of 2-chloro-4-tert-butylphenol, Eastman Kodak Company, No. P-4871, was used in the Duff reaction for the preparation of the above aldehyde. A yield of 33 g. of the aldehyde was obtained from this reaction using 100 g. of the phenol. Upon recrystallization from alcohol, pale yellow crystals were obtained; m.p.: 72°. The phenylhydrazone derivative was prepared; m.p.: 146°. 2-Hydroxy-3-chloro-5-tert-butylbenzaldehyde condensed readily with ethylenediamine in alcohol solution to form a yellow crystalline Schiff's base; m.p.: 115°.

2-Hydroxy-3-bromo-5-tert-butylbenzaldehyde. Eastman Kodak Company, 2-bromo-4-tert-butylphenol, No. P-4868, was used in the synthesis of the above aldehyde by the Duff reaction. The yield was slightly lower than in the case of the corresponding chloro- derivative just described, 25 g. being obtained from 100 g. of the phenol; m.p.: 88°. The melting points of the phenylhydrazone and oxime derivatives were 143-144° and 169° respectively. Daines and Rothrock (35) have reported 86-87° and 164° for the

melting points of this aldehyde and its oxime derivative. The Schiff's base with ethylenediamine was prepared; m.p.: 120°.

2-Hydroxy-3-isopropyl-5-chloro-6-methylbenzaldehyde. From the Duff reaction using 100 g. of p-chlorothymol 12 g. of the above aldehyde was obtained. This phenol was obtained from Eastman Kodak Company, No. 2777. The melting point of the aldehyde recrystallized from alcohol was 49°, and of its oxime derivative from this same solvent 150-151°. The Schiff's base of this aldehyde with ethylenediamine was prepared and recrystallized from alcohol; m.p.: 171°.

The Duff reaction on 2-hydroxy-4-tert-butylphenol. This reaction on 100 g. of the above phenol yielded 31 g. of a yellow crystalline aldehyde material. This phenol could yield two o-hydroxyaldehydes, 2,3-dihydroxy-5-tert-butylbenzaldehyde and 2,3-dihydroxy-6-tert-butylbenzaldehyde. Upon recrystallization from alcohol this product melted sharply at 85°. No attempt was made to separate the possible isomers. A phenylhydrazone derivative and a Schiff's base with ethylenediamine were prepared; m.p.: 160-161° and 226° respectively.

Duff reaction on 3-methyl-4-chlorophenol. This phenol was obtained from Eastman Kodak Company and the

Duff reaction run using 100 g. of the material. A yield of 36 g. of crude solid product was obtained, which upon recrystallization from alcohol melted at 99°. A phenylhydrazone and an oxime derivative were prepared; m.p.: 205° and 131-132° respectively. The Schiff's base with ethylenediamine was prepared; m.p.: 221°. Theoretically this phenol might be expected to yield both 2-hydroxy-4-methyl-5-chlorobenzaldehyde and 2-hydroxy-6-methyl-5-chlorobenzaldehyde, but it has not been definitely established whether or not such was the case. Walther and Demmelmeyer (36) have reported the preparation of one of these aldehydes, 2-hydroxy-4-methyl-5-chlorobenzaldehyde, by the Reimer-Tiemann reaction on this same phenol. The melting point reported was 68°, but no mention was made of the other possible isomer which might be expected from this reaction and no derivatives were reported.

2-Hydroxy-3,5-dibromobenzaldehyde. The Duff reaction was run on 2,4-dibromophenol obtained from Eastman Kodak Company, No. 854. From 100 g. of the phenol, only 7.5 g. of crude 2-hydroxy-3,5-dibromobenzaldehyde was obtained. The aldehyde was recrystallized from alcohol; m.p.: 75-77°. A phenylhydrazone derivative was prepared; m.p.: 141-142°. This aldehyde formed a Schiff's base with ethylenediamine which was recrystallized from n-propyl alcohol; m.p.: 247°.

2-Hydroxy-5-methylbenzaldehyde. The preparation of this aldehyde by the Reimer-Tiemann reaction has been described in a previous section. The maximum yield obtained by that reaction was 15 per cent. By the Duff reaction on 125 g. of p-cresol, 46.3 g. or almost 29 per cent yield was obtained. The melting points of the aldehyde and of the Schiff's base with ethylenediamine were 55.8 and 164° respectively.

2-Hydroxy-5-ethylbenzaldehyde. This aldehyde was prepared by the Duff reaction on p-ethylphenol. The phenol used was obtained from Dow Chemical Company; m.p.: 42°. Using 50 g. of this phenol in the Duff synthesis, 11 g. of aldehyde was obtained. The aldehyde was vacuum distilled and the purified material cooled in an ice and salt mixture until crystallized: m.p.: -5°. The phenylhydrazone and semicarbazone derivatives were prepared; m.p.: 126° and 214° respectively. Auwers (37) prepared this aldehyde by the Reimer-Tiemann reaction on p-ethylphenol. The semicarbazone derivative was also reported; m.p.: 208°.

2-Hydroxy-3-n-butoxybenzaldehyde. This aldehyde was prepared by the Duff reaction on 2-n-butoxyphenol. This phenol was prepared as follows: In a 5 liter round bottomed flask there was placed 1200 ml. of water in which had been dissolved 120 g. of sodium hydroxide. The solution was boiled for a few minutes to expel the dissolved

solved air and then 330 g. of pyrocatechol added. After the pyrocatechol had completely dissolved the solution was allowed to cool somewhat and then 420 g. of n-butylbromide added. The flask was then fitted with a reflux condenser and refluxed gently for a period of 20 hours. At the end of the refluxing period the mixture was cooled, the upper layer separated from the lower (water) layer, washed with dilute hydrochloric acid and then with water. The crude product was distilled and a fraction collected; b.p.: 150-154°/40 mm. The higher boiling material which was largely 1,2 dibutoxybenzene solidified upon cooling. A yield of 496 g. or 81 per cent of pure o-n-butoxyphenol was obtained. Slotta and Franke (38) prepared this phenol by the reaction of p-toluenesulfonic acid (n-butyl ester) on pyrocatechol; b.p.: 127°/17 mm.; 239°/760 mm. From the Duff reaction on 200 g. of this phenol, 35 g. of 2-hydroxy-3-n-butoxybenzaldehyde was obtained; m.p.: 49°. The Schiff's base of this aldehyde with ethylenediamine was prepared and recrystallized from alcohol; m.p.: 93.5°.

The more important data in regard to the compounds prepared by the Duff method which have been described in the foregoing section are summarized in Table V. The compounds listed in the last part of the table for which no references are given have not been previously reported

in the literature. Summarized in Table VI are the data in regard to those compounds obtained from the Duff reaction on phenols which might possibly produce two o-hydroxyaldehydes. Although it seems probable that the Duff reaction produces only one of the two isomers possible in such cases, as for example with m-cresol, the identity of several of these aldehydes is in some doubt, and they have therefore been grouped separately.

The remaining portion of this section, following Tables V and VI, will be devoted to a description of a few preparations which were attempted by the Duff reaction, but which did not yield any of the anticipated aldehydes.

TABLE V

Summary of Data on Aldehydes

Prepared by the Duff Reaction

	Phenol Used	Quantity	Aldehyde Obtained	Yield	M.P. or B
1.	2,5-dimethyl-phenol	25 g.	2-hydroxy-3,6-dimethyl-benzaldehyde	9.0 g.	61°
2.	3,5-dimethyl-phenol	25 g.	2-hydroxy-4,6-dimethyl-benzaldehyde	3.6 g.	48°
3.	4-methylphenol (p-cresol)	125 g.	2-hydroxy-5-methyl-benzaldehyde	46.3 g.	56°
4.	2,4-dimethyl-phenol	25 g.	2-hydroxy-3,5-dimethyl-benzaldehyde	10.0 g.	23°
5.	2-bromo-4-tert-butylphenol	100 g.	2-hydroxy-3-bromo-5-tert-butylbenzaldehyde	25.0 g.	88°
6.	2-iso-propyl-5-methylphenol (Thymol)	300 g.	2-hydroxy-3-isopropyl-6-methylbenzaldehyde	56.0 g.	100°/3.5 139°/13 m N_{25}: 1.55
7.	4-phenylphenol	200 g.	2-hydroxy-5-phenyl-benzaldehyde	31.0 g.	100°
8.	2-bromophenol	50 g.	2-hydroxy-3-bromo-benzaldehyde	5.0 g.	49°
9.	2-chlorophenol	150 g.	2-hydroxy-3-chloro-benzaldehyde	9.0 g.	52°
10.	4-ethylphenol	50 g.	2-hydroxy-5-ethyl-benzaldehyde	11.0 g.	-5°
11.	2-n-butoxyphenol	200 g.	2-hydroxy-3-n-butoxy-benzaldehyde	35.0 g.	49°

ld	M.P. or B.P.	Derivatives	Schiff's Base with Ethylene-diamine	References
0 g.	61°	Phenylhydrazone 148.5°	182°	29
6 g.	48°	Phenylhydrazone 126°	153°	27, 28
3 g.	56°		164°	41, 42 12, 19
0 g.	23°	Phenylhydrazone 103° Oxime 133°	142.5°	24, 31
0 g.	88°	Phenylhydrazone 144° Oxime 169°	120°	35
0 g.	100°/3.5 mm. 139°/13 mm. N_{25}: 1.551	Semicarbazone 194°	113°	19, 32, 7
0 g.	100°		above 250°	19, 44
0 g.	49°		152°	23, 43
0 g.	52°		174°	7, 19, 23
0 g.	-5°	Phenylhydrazone 126° Semicarbazone 214°	143°	37
0 g.	49°		93.5°	

TABLE V, Continued

	Phenol Used	Quantity	Aldehyde Obtained	Yield	M.P. or B
12.	2-tert-amylphenol	150 g.	2-hydroxy-3-tert-amylbenzaldehyde	20 g.	106°/10
13.	2-methyl-4-tert-amylphenol	200 g.	2-hydroxy-3-methyl-5-tert-amylbenzaldehyde	45 g.	108-110° /
14.	2-chloro-4-tert butylphenol	100 g.	2-hydroxy-3-chloro-5-tert-butylbenzaldehyde	33 g.	72°
15.	p-chlorothymol	100 g.	2-hydroxy-3-iso-propyl-5-chloro-6-methylbenzaldehyde	12 g.	49°
16.	2,4-dibromophenol	100 g.	2-hydroxy-3,5-dibromobenzaldehyde	7.5 g.	77°

ued

Aldehyde Obtained	Yield	M.P. or B.P.	Derivatives	Schiff's Base with Ethylene-diamine
ıydroxy-3-tert-amyl-ızaldehyde	20 g.	106°/10 mm.		109.5°
ıydroxy-3-methyl-5-'t-amylbenzaldehyde	45 g.	108-110°/1 mm.		90°
ıydroxy-3-chloro-5-'t-butylbenzaldehyde	33 g.	72°	Phenylhydrazone 146°	115°
ıydroxy-3-iso-propyl-hloro-6-methyl-ızaldehyde	12 g.	49°	Oxime 151°	171°
ıydroxy-3,5-dibromo-ızaldehyde	7.5 g.	77°	Phenylhydrazone 142°	247°

TABLE VI

Summary of Data on Aldehydes, Prepared by the Duff Reaction, Which Have Not Been Definitely Characterized

	Phenol Used	Quantity	Aldehyde Obtained	Yield	M.P. or
1.	3,4-dimethylphenol	25 g.	2-hydroxy-5,6-dimethylbenzaldehyde and/or 2-hydroxy-4,5-dimethylbenzaldehyde	14 g.	69°
2.	3-methyl-4-chlorophenol	200 g.	2-hydroxy-4-methyl-5-chlorobenzaldehyde and/or 2-hydroxy-6-methyl-5-chlorobenzaldehyde	65 g.	99°
3.	3-methyl-4-tert-butylphenol	300 g.	2-hydroxy-5-tert-butyl-6-methylbenzaldehyde and/or 2-hydroxy-5-tert-butyl-4-methylbenzaldehyde	50 g.	109-110°
4.	2-hydroxy-4-tert-butylphenol	100 g.	2,3-dihydroxy-5-tert-butylbenzaldehyde and/or 2,3-dihydroxy-6-tert-butylbenzaldehyde	31 g.	85°

ld	M.P. or B.P.	Derivatives	Schiff's Base with Ethylene-diamine	References
g.	69°		212-214°	30
g.	99°	Phenylhydrazone 205° Oxime 132°	221°	36
g.	109-110°/2 mm.		165°	
g.	85°	Phenylhydrazone 160-161°	226°	

Attempted preparation of 2-hydroxy-3,5-dinitrobenzaldehyde. The preparation of this aldehyde was attempted by means of the Duff reaction using 2,4-dinitrophenol. The phenol used was obtained from Eastman Kodak Company, T-102. The material obtained from the reaction was recrystallized from alcohol; m.p.: 109°. Hill and Robinson (39) obtained this aldehyde by the nitration of salicylaldehyde; m.p.: 62-63°. It seemed possible that the material from the Duff reaction was merely recovered phenol, even though no phenol had ever been recovered in previous instances. A mixed melting point with some of the original phenol which had been recrystallized showed the compounds to be the same. This was the first abnormal reaction obtained by the Duff method. More than 50 per cent of the original starting material was recovered. It may be mentioned that 2,4-dinitrophenol is a sufficiently strong acid to form a stable salt with ethylenediamine; m.p.: 190°. This compound was at first thought to be a Schiff's base because of its yellow crystalline character and this fact delayed for a time the identification of the product obtained. Duff (19) has also mentioned that aldehydes are not obtained when various nitro- and dinitrophenols are used, but no specific examples were given.

The Duff reaction on 3,5-dinitro-o-cresol. This phenol was obtained from Eastman Kodak Company, No. 1344.

The results obtained by the Duff synthesis on this phenol were identical to that reported in the preceding paragraph for 2,4-dinitrophenol. In this instance also a large amount of the unreacted cresol was recovered and no aldehyde was obtained. This phenol also forms a salt with ethylenediamine.

Attempted preparation of thiosalicylaldehyde. The Duff reaction was run using 50 g. of thiophenol, obtained from Eastman Kodak Company. About 1 g. of a white crystalline product was obtained which was recrystallized from alcohol; m.p.: 60°. This material did not form a derivative with phenylhydrazine or ethylenediamine, and since such a small amount was obtained no further effort was made to identify this product. Friedlander and Lenk (4) have prepared thiosalicylaldehyde by the diazotization of o-aminobenzaldehyde followed by reaction of the diazonium compound with potassium xanthate in alkaline solution. The product was reported to be a yellow liquid and to form a phenylhydrazone derivative; m.p.: 127-129°.

Attempted preparation of 2-hydroxy-3-aldehydopyridine. The Duff reaction was run using 50 g. of 2-hydroxypyridine obtained from Reilly Chemical Company. Assuming the formation of some of the desired product it was anticipated that because of the basic character of 2-hydroxy-

3-aldehydopyridine this product would not distil from an acid solution as do the o-hydroxyaldehydes. The acidified reaction mixture was therefore cooled and then neutralized with a sodium bicarbonate solution until just basic to litmus. The mixture was extracted with ether, the ether removed by distillation, and the 1 g. of the product which was obtained tested for aldehyde properties with phenylhydrazine and ethylenediamine. No reaction was obtained with either of these reagents. It was therefore concluded that the desired aldehyde had not been obtained, and not enough of the product was available to make further identification possible.

Brouns and Diehl (44) have also reported that the Duff reaction on o-hydroxybiphenyl did not yield any of the expected aldehyde.

It is not altogether surprising, when one considers the nature of some of these compounds, that no aldehydes were obtained, since these compounds differ markedly from most phenols. The general applicability and usefulness of the Duff reaction certainly is not seriously limited by these few exceptions.

CONCLUSIONS

As a result of the studies which have been made on the Reimer-Tiemann and on the Duff methods of synthesizing o-hydroxyaldehydes and from the experience gained in applying these methods to a large number of phenols, the following general conclusions have been reached.

1. The yields of o-hydroxyaldehydes obtained by the Reimer-Tiemann method are very low, usually below 10 per cent. The optimum proportions of reagents have been found to be 4 moles of chloroform, 9 moles of alkali, and 80-85 moles of water to 1 mole of the phenol.

2. Yields by the Reimer-Tiemann method may be increased very slightly by carrying out the reaction under pressure at 150-175 p.s.i.g. The increased yield amounts to only 1 or 2 per cent.

3. The method of Duff for the synthesis of o-hydroxyaldehydes from phenols is far superior to the Reimer-Tiemann method. The time required is only a fraction of that required by the latter method and the yield on the average is about 18 per cent, about double that obtained by the Reimer-Tiemann method.

4. The nature of the phenol determines to a large extent the yields obtained by either of these methods. In general, ortho- substituted phenols give very low yields,

while para- substituted phenols usually give better yields. Phenols with as many as three substituents have been found to give satisfactory yields by the Duff method. Halogenated phenols give below average yields by the method of Duff. By the Reimer-Tiemann method these phenols give only negligible yields. Mono- and dinitrophenols do not yield aldehydes by either of the methods.

5. Hexamethylenetetramine decomposes rapidly in glyceroboric acid at temperatures above 160°. In the Duff reaction therefore, both the phenol and the hexamethylenetetramine must be added simultaneously to the anhydrous glyceroboric acid medium in order to obtain the maximum yield.

6. The method of Duff has now been applied to a sufficiently large number of phenols to warrant the conclusion that it is as general a method as the Reimer-Tiemann method. The method succeeds on several phenols on which the Reimer-Tiemann method fails. It may prove to be the more valuable method inasmuch as in several cases dialdehydes may also be synthesized.

7. The Duff reaction is not applicable to nitrophenol, dinitrophenol, thiophenol, or to 2-hydroxypyridine.

8. The Schiff's bases of o-hydroxyaldehydes and ethylenediamine are yellow crystalline compounds with sharp melting points, and may therefore serve as derivatives for these aldehydes. These derivatives are more easily prepared and recrystallized than are the common derivatives such as semicarbazones, oximes, and phenylhydrazones.

SUMMARY

A survey of the proposed mechanisms for the Reimer-Tiemann reaction is presented. This method for the preparation of o-hydroxyaldehydes has been studied and the optimum reagent ratios established. This reaction may also be carried out under pressure at 175 p.s.i.g. with a very small increase in yield resulting.

The method of Duff has been slightly modified to give improved yields of o-hydroxyaldehydes from phenols. This method has been found to be very general, is more rapid, more convenient, and gives better yields than the Reimer-Tiemann method. A few limitations of this reaction were found.

A large number of o-hydroxyaldehydes, several of which are new, have been prepared by the Duff reaction. Appropriate derivatives of these aldehydes have been prepared and the important physical constants of both the aldehydes and derivatives have been determined.

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